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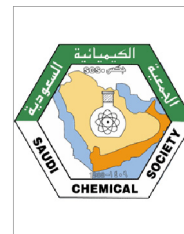
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## ORIGINAL ARTICLE

# Lactamomethylation of alkylphenols: Synthesis and quantum-chemical study of the reaction pathway



Stepan V. Vorobyev<sup>a,\*</sup>, Olga V. Primerova<sup>a</sup>, Sergey Yu. Bylikin<sup>b</sup>,  
Vladimir N. Koshelev<sup>a</sup>

<sup>a</sup> Department of Organic Chemistry and Petroleum Chemistry, Faculty of Chemical and Environmental Engineering, Gubkin University, Moscow, Russia

<sup>b</sup> The Open University, Walton Hall, Milton Keynes, MK7 6AA, UK

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Quantum-chemical calculations;  
Mechanism study

**Abstract** Six novel lactamomethyl derivatives of 2,5-dimethylphenol and 2,3,5-trimethylphenol were prepared with moderate yields by the reaction of corresponding phenols with 1-(hydroxymethyl)lactams in the presence of an acid catalyst. In all cases, the substitution occurred at position 4 to the phenolic hydroxyl group. The structures of all synthesized compounds were confirmed by FT-IR, <sup>1</sup>H and <sup>13</sup>C NMR, 2D NMR and elemental analysis. The selectivity and possible pathways of the lactamomethylation reaction were studied by quantum-chemical methods. *In silico* calculations showed that the substitution at *para*-position to the hydroxyl group of the corresponding phenols was more preferable due to the higher stability of forming intermediates.

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## 1. Introduction

Oxidation affects the properties of fuels and lubricating oils, leading to corrosion and premature wear of equipment. Oxidation is a radical process that can be inhibited by antioxidants (Burton and Ingold, 1981), such as phenols (Shahidi et al., 1992). Naturally occurring and synthetic phenols are widely used as additives to biofuels (Varatharajan and Pushparani,

2018, Uğuz et al., 2019), pharmaceuticals (Tsai and Lee, 2008, Soto et al., 2017) and foods (Raccach, 1984, Medeiros et al., 2010) because of their ability to interrupt chain reactions by forming stable radicals that do not oxidize organic compounds (Leopoldini et al., 2004). These stable radicals can also react with hydroperoxides formed by auto-oxidation (Ingold, 1961). Electron-donating substituents in phenyl ring enhance the antioxidant properties by facilitating the transfer of the hydrogen atom from the OH group to free radicals (Torres de Pinedo et al., 2007, Osipova et al., 2020). In addition, phenols exhibit diverse biological activity, including antimicrobial (Magnani et al., 2014), antitumor (Ryu et al., 1994, Nile et al., 2017) and analgesic (Hidaka et al., 1986, Pawełczyk et al., 2020).

The use of phenols as additives in lubricating oils is limited by their thermal stability (Santos et al., 2012), which can be

\* Corresponding author.

E-mail address: [vorstepan@yandex.ru](mailto:vorstepan@yandex.ru) (S.V. Vorobyev).  
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increased by introducing a heterocyclic moiety to the phenyl ring (Koshelev et al., 1995). We have previously reported (Vorobyev et al., 2018, Vorobyev et al., 2019) the synthesis of lactamomethyl derivatives of phenols. Lactams were chosen as heterocyclic fragments due to their nootropic (Ostrovskaya et al., 1993, Berestovitskaya et al., 2018), antihypoxic (Bakibaev et al., 1997), anticonvulsant (Malawska, 2005) and other biological effects (Saldívar-González et al., 2019). In particular, we demonstrated that the introduction of a lactamomethyl fragment to the phenyl ring generally decreases the energy of the ArO–H bond, enhancing the antioxidant properties (Vorobyev et al., 2018).

Amidoalkyl derivatives of phenols (in particular, lactamomethyl ones) can be synthesized by Tscherniak–Einhorn reaction (Mudududdla et al., 2012, Schramm et al., 2015). Tscherniak–Einhorn reaction is a type of Mannich reaction, so similar compounds containing moieties of nitrogen heterocycles can be produced by Mannich reaction (Yo. Omura et al., 2001; Biersack et al., 2018, Farooq et al., 2021). Aminomethylation of alkylphenols, such as thymol and 2,3,5-trimethylphenol, has also been reported (Strubell and Baumgärtel, 1962, Burckhalter et al., 1946). These phenols have two possible reaction sites (*ortho*- and *para*-positions to the hydroxyl group), but the composition of target compounds was confirmed by elemental analysis only, leaving the question of the reaction selectivity unanswered. Later it was shown that thymol can form either *ortho*- or *para*-substituted products, depending on the structure of the amine reactant (Inci Gul et al., 2016).

Although the mechanism of Tscherniak–Einhorn reaction was studied previously (Zaugg et al., 1969, Barry et al., 1977) for some amides, there is a lack of such information about lactamomethylation of aromatic compounds and especially phenols.

In this work we report the synthesis of lactamomethyl derivatives of alkylphenols and quantum-chemical study of the possible reaction pathways.

## 2. Material and methods

### 2.1. Measurement and reagents

In this article, 2,5-dimethylphenol (compound 1) and 2,3,5-trimethylphenol (compound 2) were the substrates for the lactamomethylation reaction. Common reagents and solvents were purchased from Acros and Sigma–Aldrich. 1-(hydroxymethyl)pyrrolidin-2-one, 1-(hydroxymethyl)azepan-2-one, 1-(hydroxymethyl)piperidin-2-one were synthesized as described previously (Vorobyev et al., 2018). The melting points were determined using a Stuart SMP30 instrument. The IR spectra were recorded using an Agilent Carry 600 spectrometer equipped with an attenuated total reflectance (ATR) device. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at ambient temperature using a Bruker Avance II 300 spectrometer ( $^1\text{H}$ , 300 MHz;  $^{13}\text{C}$ , 75 MHz) in  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$  was used as the internal reference. 2D NMR spectra were recorded using a Bruker Avance II 600 instrument ( $^1\text{H}$ , 600 MHz;  $^{13}\text{C}$ , 150 MHz) under the same conditions. Elemental analysis was performed using a Vario MicroCube apparatus.

### 2.2. General procedure for the preparation of lactamomethyl derivatives of alkylphenols

A solution of the corresponding phenol (0.01 mol), 1-(hydroxymethyl)lactam (0.01 mol) and trifluoroacetic acid (4 mL) in chloroform (20 mL) was refluxed for 48 h, then the reaction mixture was cooled and poured into toluene (75 mL). The resulting solution was washed with aqueous sodium bicarbonate to neutral pH. The organic layer was dried over calcined magnesium sulfate, and the volatiles were removed in vacuum. The residue was allowed to crystallize under hexane, and the product was recrystallized from toluene/cyclohexane (2:1).

#### 2.2.1. 1-(4-hydroxy-2,5-dimethylbenzyl)pyrrolidin-2-one (3)

White powder with m.p. 158–159 °C (yield 51%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm,  $^3J_{\text{HH}}$ , Hz): 1.98 (p, 2H, 4- $\text{CH}_2$  in lactam,  $J = 6.6$ ); 2.21 (s, 6H, two Ar- $\text{CH}_3$ ); 2.49 (t, 2H, 3- $\text{CH}_2$  in lactam,  $J = 7.7$ ); 3.22 (3, 2H, 5- $\text{CH}_2$  in lactam,  $J = 6.6$ ); 4.41 (s, 2H, Ar- $\text{CH}_2$ -N); 6.71 (s, 1H, Ar-H); 6.90 (s, 1H, Ar-H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 15.52 (Ar- $\text{CH}_3$  at position 2); 17.66 (4- $\text{CH}_2$  in lactam); 18.91 (Ar- $\text{CH}_3$  at position 5); 31.21 (3- $\text{CH}_2$  in lactam); 44.47 (N- $\text{CH}_2$ Ar), 46.65 (5- $\text{CH}_2$  in lactam); 117.10 (6-C in phenyl ring), 121.66 (2-C in phenyl ring), 124.83 (4-C in phenyl ring), 132.34 (3-C in phenyl ring), 135.40 (5-C in phenyl ring), 154.44 (1-C in phenyl ring); 175.05 ( $\text{C} = \text{O}$ ).

FT-IR,  $\nu$ ,  $\text{cm}^{-1}$ : 3186 (O–H), 1660 ( $\text{C} = \text{O}$ ), 1573 ( $\text{C} = \text{C}$ ), 1511 ( $\text{C}-\text{C}$ ), 1294 (Car–O).

Calc., %: C 71.21, H 7.81, N 6.39. Found, %: C 71.67, H 7.69, N 6.28.  $\text{C}_{13}\text{H}_{17}\text{NO}_2$

#### 2.2.2. 1-(4-hydroxy-2,5-dimethylbenzyl)piperidin-2-one (4)

White powder with m.p. 171–172 °C (yield 67%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm,  $^3J_{\text{HH}}$ , Hz): 1.77 (m, 4H, 4,5- $\text{CH}_2$  in lactam); 2.17 (s, 3H, Ar- $\text{CH}_3$ ); 2.19 (s, 3H, Ar- $\text{CH}_3$ ); 2.49 (t, 2H, 3- $\text{CH}_2$  in lactam,  $J = 6.0$ ); 3.10 (t, 2H, 6- $\text{CH}_2$  in lactam,  $J = 5.5$ ); 4.57 (s, 2H, Ar- $\text{CH}_2$ -N); 6.67 (s, 1H, Ar-H); 6.84 (s, 1H, Ar-H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 15.59 (Ar- $\text{CH}_3$  at position 2); 19.00 (Ar- $\text{CH}_3$  at position 5); 21.18 (4- $\text{CH}_2$  in lactam); 23.05 (5- $\text{CH}_2$  in lactam); 32.26 (3- $\text{CH}_2$  in lactam); 46.57 (N- $\text{CH}_2$ Ar), 47.53 (6- $\text{CH}_2$  in lactam); 117.13 (6-C in phenyl ring), 121.48 (2-C in phenyl ring), 125.28 (4-C in phenyl ring), 131.91 (3-C in phenyl ring), 135.39 (5-C in phenyl ring), 154.22 (1-C in phenyl ring); 170.17 ( $\text{C} = \text{O}$ ).

FT-IR,  $\nu$ ,  $\text{cm}^{-1}$ : 3391 (O–H), 1622 ( $\text{C} = \text{O}$ ), 1602 ( $\text{C} = \text{C}$ ), 1251 ( $\text{C}-\text{O}$ ), 1072 (Car–O).

Calc., %: C 72.07, H 8.21, N 6.00. Found, %: C 72.59, H 7.99, N 5.98.  $\text{C}_{14}\text{H}_{19}\text{NO}_2$

#### 2.2.3. 1-(4-hydroxy-2,5-dimethylbenzyl)azepan-2-one (5)

White powder with m.p. 177–179 °C (yield 59%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm,  $^3J_{\text{HH}}$ , Hz): 1.42 (m, 2H, 5- $\text{CH}_2$  in lactam); 1.69 (m, 4H, 4,6- $\text{CH}_2$  in lactam); 2.19 (s, 6H, two Ar- $\text{CH}_3$ ); 2.62 (m, 2H, 3- $\text{CH}_2$  in lactam); 3.24 (t, 2H, 7- $\text{CH}_2$  in lactam,  $J = 4.5$ ); 4.53 (s, 2H, Ar- $\text{CH}_2$ -N); 6.67 (s, 1H, Ar-H); 6.85 (s, 1H, Ar-H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 15.57 (Ar- $\underline{\text{CH}}_3$  at position 2); 19.02 (Ar- $\underline{\text{CH}}_3$  at position 5); 23.40 (4- $\underline{\text{CH}}_2$  in lactam); 27.70 (5- $\underline{\text{CH}}_2$  in lactam); 29.91 (6- $\underline{\text{CH}}_2$  in lactam); 37.11 (3- $\underline{\text{CH}}_2$  in lactam); 47.58 ( $\text{NCH}_2\text{Ar}$ ), 48.23 (7- $\underline{\text{CH}}_2$  in lactam); 117.19 (6-C in phenyl ring), 121.42 (2-C in phenyl ring), 125.81 (4-C in phenyl ring), 132.37 (3-C in phenyl ring), 135.50 (5-C in phenyl ring), 154.21 (1-C in phenyl ring); 176.18 ( $\underline{\text{C}} = \text{O}$ ).

FT-IR,  $\nu$ ,  $\text{cm}^{-1}$ : 3410 (O-H), 1632 ( $\text{C} = \text{O}$ ), 1612 ( $\text{C} = \text{C}$ ), 1261 (C-O), 1045 (Car-O).

Calc., %: C 72.84, H 8.56, N 5.66. Found, %: C 72.59, H 8.79, N 5.41.  $\text{C}_{15}\text{H}_{21}\text{NO}_2$

#### 2.2.4. 1-(4-hydroxy-2,3,6-trimethylbenzyl)pyrrolidin-2-one (6)

White powder with m.p. 163–165 °C (yield 62%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm,  $^3J_{\text{HH}}$ , Hz): 1.92 (p, 2H, 4- $\underline{\text{CH}}_2$  in lactam,  $J = 6.8$ ); 2.17 (s, 3H, Ar- $\underline{\text{CH}}_3$ ); 2.22 (s, 3H, Ar- $\underline{\text{CH}}_3$ ); 2.27 (s, 3H, Ar- $\underline{\text{CH}}_3$ ); 2.47 (t, 2H, 3- $\underline{\text{CH}}_2$  in lactam,  $J = 7.8$ ); 3.09 (t, 2H, 5- $\underline{\text{CH}}_2$  in lactam,  $J = 6.8$ ); 4.54 (s, 2H, Ar- $\underline{\text{CH}}_2\text{-N}$ ); 6.59 (s, 1H, Ar-H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 12.00 (Ar- $\underline{\text{CH}}_3$  at position 2); 16.05 (Ar- $\underline{\text{CH}}_3$  at position 3); 17.85 (4- $\underline{\text{CH}}_2$  in lactam); 20.21 (Ar- $\underline{\text{CH}}_3$  at position 5); 31.22 (3- $\underline{\text{CH}}_2$  in lactam); 40.79 ( $\text{NCH}_2\text{-Ar}$ ); 45.78 (5- $\underline{\text{CH}}_2$  in lactam); 114.76 (6-C in phenyl ring); 120.92 (2-C in phenyl ring); 123.62 (4-C in phenyl ring); 135.76 (5-C in phenyl ring); 138.08 (3-C in phenyl ring); 153.57 (1-C in phenyl ring); 174.69 ( $\underline{\text{C}} = \text{O}$ ).

FT-IR,  $\nu$ ,  $\text{cm}^{-1}$ : 3154 (O-H), 1655 ( $\text{C} = \text{O}$ ), 1592 ( $\text{C} = \text{C}$ ), 1250 (C-C), 1093 (Car-O).

Calc., %: C 72.07, H 8.21, N 6.00. Found, %: 71.81, H 8.39, N 6.02.  $\text{C}_{14}\text{H}_{19}\text{NO}_2$ .

#### 2.2.5. 1-(4-hydroxy-2,3,6-trimethylbenzyl)piperidin-2-one (7)

White powder with m.p. 222–225 °C (yield 52%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm,  $^3J_{\text{HH}}$ , Hz): 1.61–1.83 (m, 4H, 4,5- $\underline{\text{CH}}_2$  in lactam); 2.17 (s, 6H, two Ar- $\underline{\text{CH}}_3$ ); 2.23 (s, 3H, Ar- $\underline{\text{CH}}_3$ ); 2.46 (t, 2H, 2H, 3- $\underline{\text{CH}}_2$  in lactam,  $J = 6.2$ ); 2.89 (t, 2H, 6- $\underline{\text{CH}}_2$  in lactam,  $J = 5.5$ ); 4.73 (s, 2H, Ar- $\underline{\text{CH}}_2\text{-N}$ ); 6.58 (s, 1H, Ar-H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 11.99 (Ar- $\underline{\text{CH}}_3$  at position 2); 16.05 (Ar- $\underline{\text{CH}}_3$  at position 3); 20.33 (Ar- $\underline{\text{CH}}_3$  at position 5); 21.17 (4- $\underline{\text{CH}}_2$  in lactam); 23.18 (5- $\underline{\text{CH}}_2$  in lactam); 32.39 (3- $\underline{\text{CH}}_2$  in lactam); 43.33 ( $\text{NCH}_2\text{Ar}$ ); 44.59 (6- $\underline{\text{CH}}_2$  in lactam);

114.70 (6-C in phenyl ring); 120.84 (2-C in phenyl ring); 124.08 (4-C in phenyl ring); 136.18 (5-C in phenyl ring); 138.45 (3-C in phenyl ring); 153.39 (1-C in phenyl ring); 169.88 ( $\underline{\text{C}} = \text{O}$ ).

FT-IR,  $\nu$ ,  $\text{cm}^{-1}$ : 3435 (O-H), 1609 ( $\text{C} = \text{O}$ ), 1593 ( $\text{C} = \text{C}$ ), 1242 (Car-O).

Calc., %: C 72.84, H 8.56, N 5.66. Found, %: C 72.61, H 8.83, N 5.33.  $\text{C}_{15}\text{H}_{21}\text{NO}_2$

#### 2.2.6. 1-(4-hydroxy-2,3,6-trimethylbenzyl)azepan-2-one (8)

Yellow powder with m.p. 143–145 °C (yield 68%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm,  $^3J_{\text{HH}}$ , Hz): 1.33 (m, 2H, 5- $\underline{\text{CH}}_2$  in lactam); 1.67 (m, 4H, 4,6- $\underline{\text{CH}}_2$  in lactam); 2.16 (s, 3H, Ar- $\underline{\text{CH}}_3$ ); 2.18 (s, 3H, Ar- $\underline{\text{CH}}_3$ ); 2.23 (s, 3H, Ar- $\underline{\text{CH}}_3$ ); 2.59 (t, 2H, 3- $\underline{\text{CH}}_2$  in lactam,  $J = 5.9$ ); 3.02 (m, 2H, 7- $\underline{\text{CH}}_2$  in lactam,  $J = 5.9$ ); 4.66 (s, 2H, Ar- $\underline{\text{CH}}_2\text{-N}$ ); 6.61 (s, 1H, Ar).

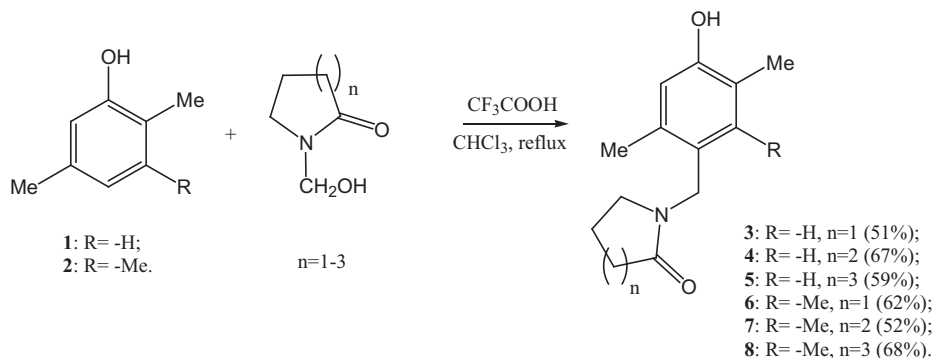
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , ppm): 12.06 (Ar- $\underline{\text{CH}}_3$  at position 2); 16.16 (Ar- $\underline{\text{CH}}_3$  at position 3); 20.32 (Ar- $\underline{\text{CH}}_3$  at position 5); 23.42 (4- $\underline{\text{CH}}_2$  in lactam); 27.85 (5- $\underline{\text{CH}}_2$  in lactam); 29.94 (6- $\underline{\text{CH}}_2$  in lactam); 37.25 (3- $\underline{\text{CH}}_2$  in lactam); 43.55 ( $\text{NCH}_2\text{Ar}$ ); 45.36 (7- $\underline{\text{CH}}_2$  in lactam); 114.84 (6-C in phenyl ring); 123.00 (2-C in phenyl ring); 124.22 (4-C in phenyl ring); 136.05 (5-C in phenyl ring); 138.39 (3-C in phenyl ring); 153.71 (1-C in phenyl ring); 176.14 ( $\underline{\text{C}} = \text{O}$ ).

FT-IR,  $\nu$ ,  $\text{cm}^{-1}$ : 3442 (O-H), 1616 ( $\text{C} = \text{O}$ ), 1596 ( $\text{C} = \text{C}$ ), 1280 (Car-O).

Calc., %: C 73.53, H 8.87, N 8.36. Found, %: 73.69, H 9.01, N 8.08.  $\text{C}_{16}\text{H}_{23}\text{NO}_2$ .

#### 2.3. Computational details

Quantum-chemical calculations were performed using Gaussian09 software (Gaussian 09, Revision D.01); the results were visualized by GaussView 6.0.16 (Roy D. Dennington II et al., 2016). Geometry optimization was carried out with the M06-2X functional using the 6-311G(d,p) basis set. The influence of solvation on  $\sigma$ -complexes stability was studied with IEF-PCM model with M06-2X functional and 6-311G(d,p) basis set. The M06-2X functional was chosen for studying the lactamomethylation pathway because it was used previously for the aromatic electrophilic substitution calculations and produced better results (in thermochemistry, kinetics and non-covalent interactions) than B3LYP (Oliveira and Esteves, 2011,



**Scheme 1** Lactamomethylation of 2,5-dimethylphenol 1 and 2,3,5-trimethylphenol 2.

Liljenberg et al., 2017). The optimized geometries were characterized by minima on the potential energy surface (PES) with no imaginary vibrational frequencies, whereas the transition states were characterized by the presence of a single imaginary frequency. Transition state calculations were carried out using synchronous transit-guided quasi-Newton (STQN) method (QST2) based on optimized structures of the reactant and product. All calculations were carried out for the gas phase ( $T = 298.15$  K,  $P = 1$  atm). Intrinsic reaction coordinate (IRC) calculations were provided to confirm that the transition state indeed connects the reactants and the products.

NBO analysis for the starting phenols was carried out with the B3LYP method using 6-311G(d,p) basis set in gas phase, as this method was previously shown (Metri et al., 2012) to give the most accurate results.

Vibration frequencies were calculated with B3LYP DFT method in 6-311 + G (2d,p) basis set. These calculations were performed for a free molecule in vacuum, while the experimental frequencies are in the solid state. In order to improve the agreement with the experimental data, theoretical values were scaled with 0.9613 (Razak et al., 2015), which allows to consider the formation of hydrogen bonds. Theoretical vibrational spectra of the target compounds were interpreted by means of potential energy distribution (PED) with VEDA program (Jamroz, 2010).

NMR chemical shifts for target compounds were calculated by B3LYP/6-311 + G (2d,p). The obtained data were scaled

according to CHESHIRE CCAT method (Lodewyk et al., 2012), combining gas-phase optimization and SMD-solvation (chloroform) model for NMR calculations. B3LYP/6-311 + G (2d,p) was chosen due to its high root mean square deviation value. Theoretical and experimental chemical shifts were compared, the agreement between them was estimated by calculation of mean absolute deviation (MAD) and root-mean-square (RMS) deviation.

### 3. Results and discussion

#### 3.1. Synthesis of the target compounds

In our previous work (Vorobyev et al., 2018) we synthesized a series of lactamomethyl derivatives of 2,4-di-*tert*-butylphenol and thymol. In the first case there was only one expected product while thymol could produce two possible isomers. According to  $^1\text{H}$  NMR data, the substitution took place at position 4 (*para*-) to the hydroxyl group. Quantum-chemical study of the lactamomethylation of thymol was also considered (Vorobyev et al., 2021).

In this work, we continued the study of lactamomethylation and synthesized novel derivatives of 2,5-dimethyl- and 2,3,5-trimethylphenols (1 and 2, respectively), which also had two possible reaction sites (Scheme 1). For the both phenols, *para*-substitution was observed.

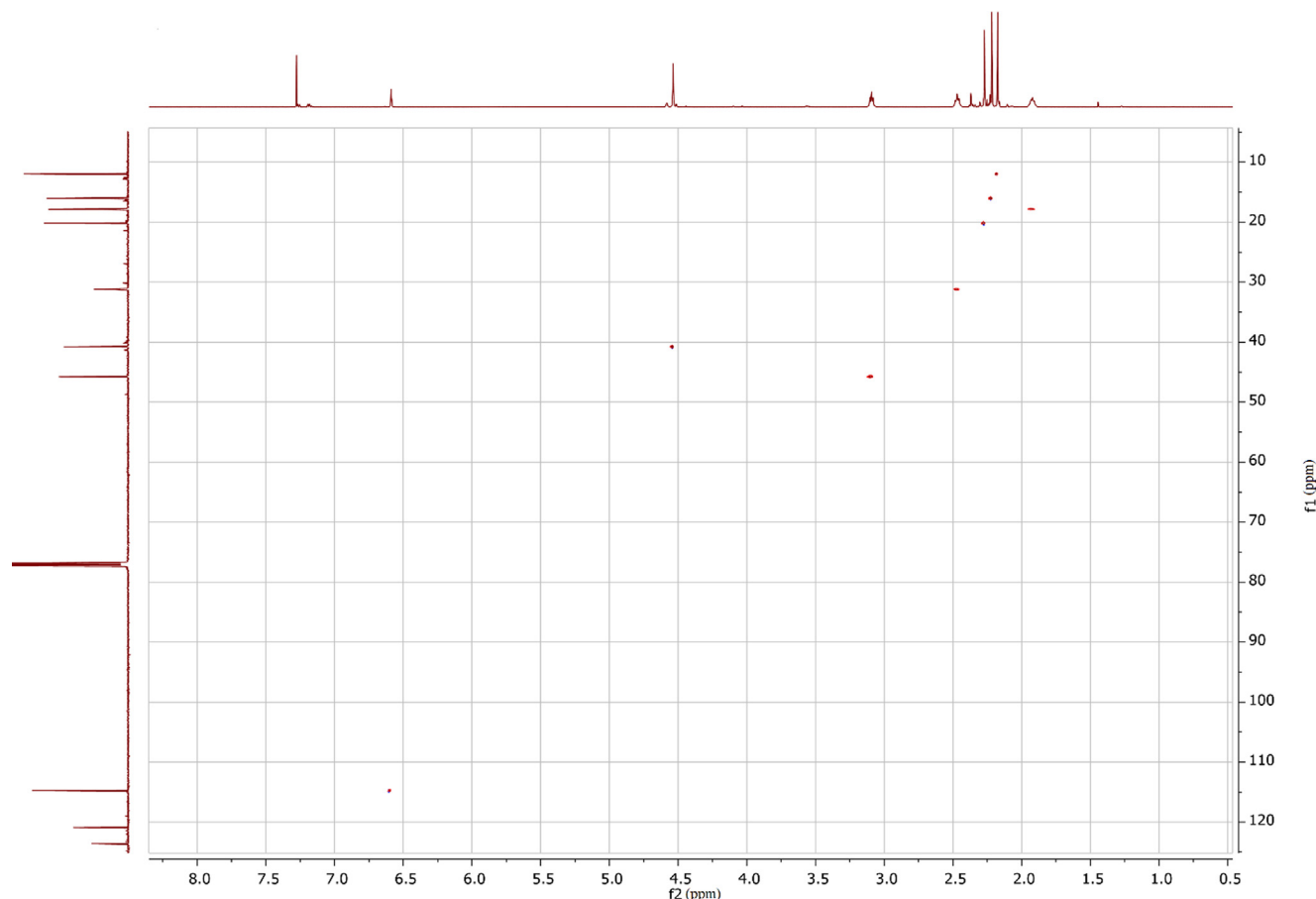


Fig. 1 HSQC ( $^1\text{H}$ ,  $^{13}\text{C}$ ) spectrum of compound 10.



Lactamomethyl derivatives of alkylphenols can also be obtained in acetic acid saturated with gaseous HCl (Idel et al., 1979). We have found that under these conditions the reaction of 1-(hydroxymethyl)pyrrolidine-2-one with 2,3,5-trimethylphenol 2 gives the same product 6 as at reflux in chloroform (Scheme 1), experimental procedure is given in [Supplementary Materials](#). Since the yields and reaction times were almost identical for both methods, we can assume that solvation does not play an important role in this reaction.

### 3.2. IR spectra

The vibrational assignments of the normal modes were made using the PED. In the FT-IR spectra of the synthesized compounds, the absorptions of C=O bonds in lactam rings were observed between 1655 and 1615  $\text{cm}^{-1}$ , which correlates with literature and calculated data (Pretsch et al., 2000, Kuruvilla et al., 2018). Broad bands of stretching vibrations of hydroxyl groups in substituted phenols were observed at 3450–3150  $\text{cm}^{-1}$ . The medium intensity bands at 1573–1612  $\text{cm}^{-1}$  and 1455–1510  $\text{cm}^{-1}$  were assigned to stretching vibrations of aromatic rings. Strong bands of stretching vibrations of C-O in phenol rings were observed at 1251–1294 and 1093–1045  $\text{cm}^{-1}$ . The out-of-plane deformational vibrations of the C-H bonds in aromatic rings were observed at 900–855  $\text{cm}^{-1}$  (Muthu and Renuga, 2014). The

experimental IR spectra generally correlate well with the calculated ones. Observed and calculated IR spectra, IR bands with scaled wavenumbers and assignments are given in [supplementary materials](#).

### 3.3. NMR spectra

The  $^1\text{H}$  NMR spectra of 2,5-dimethylphenol derivatives 3–5 had two singlets at 6.60–6.85 ppm, suggesting that the electrophilic substitution took place at position 4 to hydroxyl group.

The  $^{13}\text{C}$  NMR spectra showed all the expected signals. The lowest  $^{13}\text{C}$  chemical shifts of carbonyl groups (ca. 170 ppm) were observed for valerolactam derivatives and the highest (ca. 176 ppm) for caprolactam derivatives.

These data are in agreement with theoretical values obtained by DFT calculations. The largest deviation from experimental chemical shift for  $^1\text{H}$  calculated values is observed for the compound 8, while  $^{13}\text{C}$  shows the maximum deviation in case of 5. Tables of calculated and experimental chemical shifts, mean absolute deviations (MAD) and root-mean-square (RMS) deviations are listed in [Supplementary materials](#).

Compounds 6–8 have only one hydrogen atom in the phenyl ring and it has no visible interactions to the other protons. Unfortunately, even DFT calculations of chemical shifts for

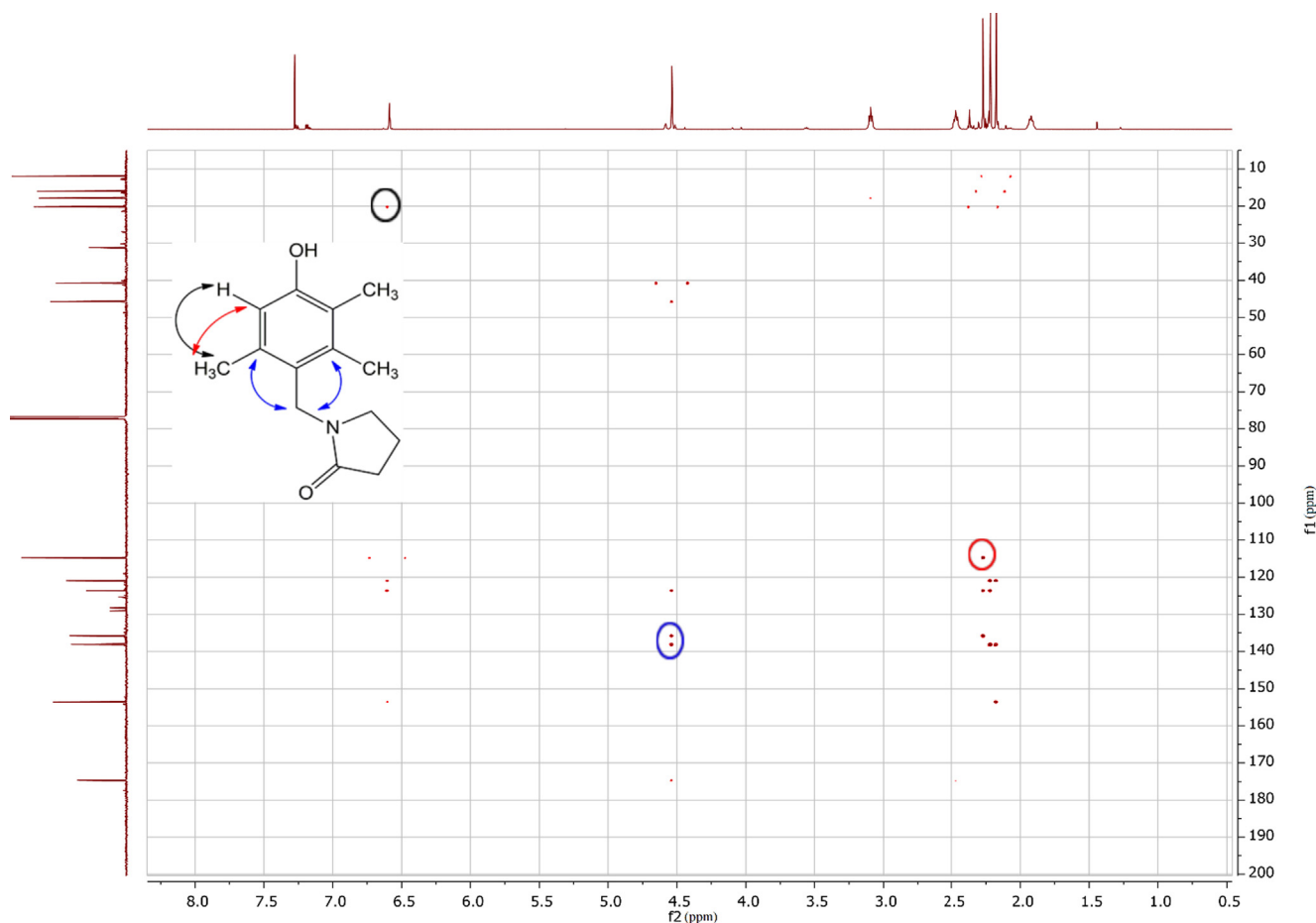
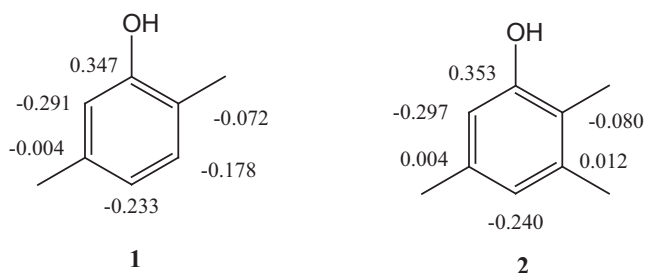


Fig. 2 HMBC ( $^1\text{H}$ ,  $^{13}\text{C}$ ) spectrum of compound 6.



**Fig. 3** Partial NBO atomic charges in 2,5-dimethylphenol 1 and 2,3,5-trimethylphenol 2.

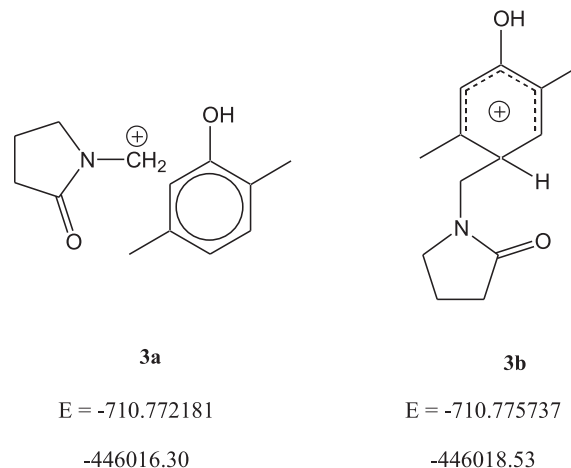
Frontier orbitals analysis showed that the Highest Occupied Molecular Orbital (HOMO) is located on the carbon atoms of the phenyl ring (Fig. 4).

*ortho*- and *para*-isomers of the compound 6 are nearly identical. However, the substitution is likely to take place at position 4 because of the lower MAD and RMS values for *para*-isomer in  $^1\text{H}$ -shift calculations (0.15 and 0.18, respectively, compared to 0.2 and 0.25 for the *ortho*-isomer). For  $^{13}\text{C}$  calculations this difference is even greater: 1.53 and 1.73 vs. 2.11 and 2.51 for *para*- and *ortho*-isomers, respectively.

In order to determine the structures of 6–8 we used 2D NMR methods. In particular, the HSQC ( $^1\text{H}$ ,  $^{13}\text{C}$ ) spectrum was used to establish single-bond correlations between hydrogen and carbon atoms (Fig. 1). The increment calculations for the  $^{13}\text{C}$  NMR spectra (Pretsch et al., 2000) also suggested that the substitution took place at position 4.

The HMBC ( $^1\text{H}$ ;  $^{13}\text{C}$ ) spectrum (Fig. 2) was used to assign the signals to specific methyl groups. The  $^1\text{H}$  signal at 2.17 ppm belongs to hydrogen atoms of the methyl group at position 2, which interact with carbon 1 of the aromatic ring (cross-peak 2.17, 153.57). They also interact with carbons 2 and 3 (2.17, 120.92 and 2.17, 138.08, respectively). The  $^1\text{H}$  signal at 2.22 ppm is produced by hydrogen atoms of the methyl group at position 3, as it shows similar correlations (2.22, 120.92 and 2.22, 138.08). Thus, the signal at 2.27 ppm belongs to hydrogen atoms of the methyl group at position 5.

In the case of *ortho*-substitution, the HMBC spectrum would show  $^2J_{\text{CH}}$  correlations between the single aromatic hydrogen atom and two aromatic carbon atoms bonded to



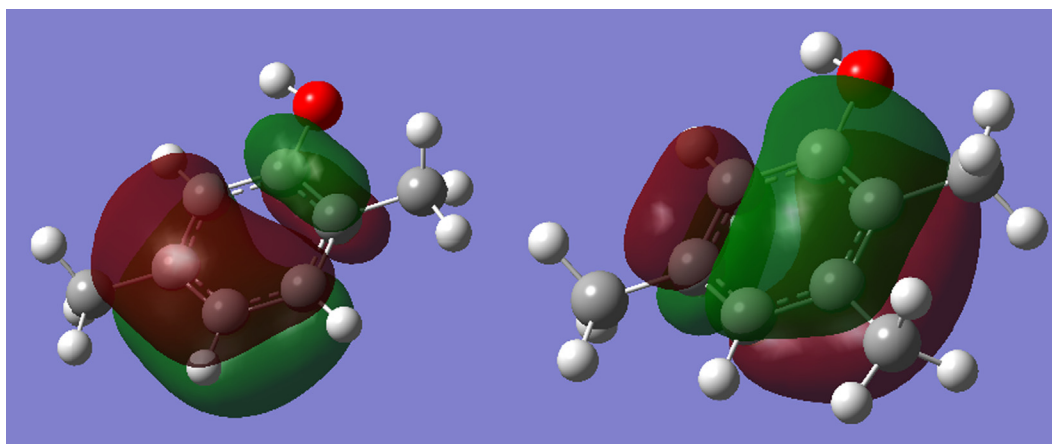
**Fig. 5** Zero-point corrected energy values (atomic units, a.u. and kcal/mol, underlined) for 2,5-dimethylphenol intermediates.

methyl groups. Furthermore,  $^3J_{\text{CH}}$  correlations between the aromatic hydrogen atom and two carbon atoms of adjacent methyl groups would also be observed.

In contrast, HMBC ( $^1\text{H}$ ,  $^{13}\text{C}$ ) spectrum (Fig. 2) shows the following  $^3J_{\text{CH}}$  correlations: (6.59, 20.21) between the aromatic proton and the carbon atom of the methyl group at position 5; (2.27, 114.76) between hydrogen atoms of the methyl group at position 5 and the carbon atom with the aromatic hydrogen; (4.54, 135.76) and (4.54, 138.08), which correspond to the interactions of hydrogen atoms of the “methylene bridge” between phenyl and lactam rings with two carbon atoms in the phenyl ring linked to methyl groups. These correlations suggest that the substitution in the phenyl ring took place at position 4 (*para*-) to hydroxyl group.

### 3.4. Quantum-chemical calculations

Lactamomethylation of aromatic compounds is an electrophilic substitution reaction, since it is a variant of amidalkylation (similar to Tscherniak-Einhorn reaction) (Barry et al., 1977, Chung et al., 2008). As it was mentioned above,



**Fig. 4** HOMO localization in 2,5-dimethylphenol 1 and 2,3,5-trimethylphenol 2.

we assumed that solvation had little effect on the reaction progress, so all quantum-chemical calculations were performed for the gas phase to reduce the computation time.

In order to study the mechanism of lactamomethylation of phenols we firstly estimated partial atomic charges and localization of frontier orbitals in starting phenols.

For the two considered phenols (2,5-dimethylphenol 1 and 2,3,5-trimethylphenol 2) the obtained results were very similar. The greatest negative partial charge (NBO scheme) was located on the carbon atom at *ortho*-position to the hydroxyl group in each compound, although the charge at *para*-position had comparable value (Fig. 3):

As a result, the analysis of the partial charge distribution and MO localization shows that the pathway of lactamomethylation cannot be predicted properly by static factors, such as electron structures of the reactants. Another key parameter for electrophilic substitution is the stability of the intermediates (dynamic factor). The reaction is likely to proceed through the formation of the lowest-energy intermediate. Previously it was shown (Shi, 2017) that the zero-point corrected energies of the reaction system could be used to estimate the pathway of the reaction.

We assumed that lactamomethylation involves typical steps (Liljenberg et al., 2010; Liljenberg et al., 2017) for the electrophilic substitution: formation of the  $\pi$ -complex, followed by the  $\sigma$ -complex through the transition state (TS) with subsequent formation of the products via another transition state. Firstly, we considered the reaction of 2,5-dimethylphenol 1 with the pyrrolidone derivative.

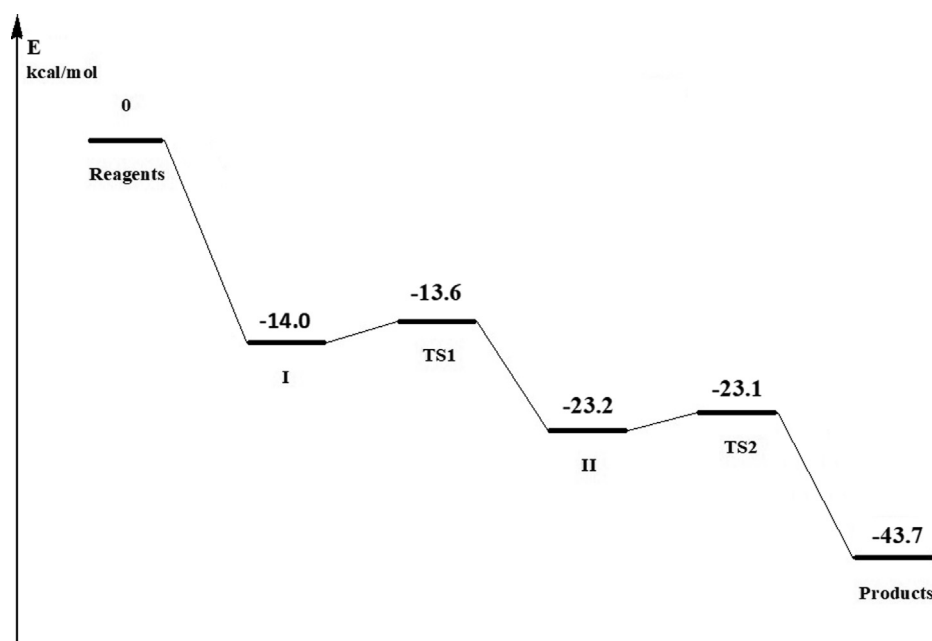
The comparison of the two possible intermediates for 1 shows that the  $\sigma$ -complex at *para*-position (3b) is more stable, with the energy 2.2 kcal/mol (9.22 kJ/mol) lower than that for the complex at *ortho*-position (3a, Fig. 5). Moreover, in the case of *ortho*-substitution the energy minimum corresponds not to the  $\sigma$ -complex but to the  $\pi$ -complex, which does not lead to the formation of the expected bond. Both complexes

have no imaginary frequencies, so they represent true energy minima.

The energy profile of the reaction of 2,5-dimethylphenol 1 with the pyrrolidone derivative at *para*-position (Fig. 6) shows that the formation of the  $\pi$ -complex (I) significantly decreases the energy of the system by 14.0 kcal/mol (58.8 kJ/mol) compared to reactants. The transition state (TS1) for the conversion into  $\sigma$ -complex (II) is very close in energy to the  $\pi$ -complex (the difference is only 0.4 kcal/mol, or 1.68 kJ/mol), so the barrier for conversion into (II) is very low. TS1 is characterized by one imaginary frequency ( $-115\text{ cm}^{-1}$ ). The intermediate  $\sigma$ -complex has a free energy that is 9.6 kcal/mol (40.2 kJ/mol) lower than that of the TS1. The formation of the products is preceded by the second transition state (TS2) with the imaginary frequency of  $-137\text{ cm}^{-1}$ . As the TS1 is similar to I, TS2 has similar energy to the  $\sigma$ -complex II.

A similar picture is observed for other target compounds (3–8). The substitution proceeds through the more stable  $\sigma$ -complex, which forms in the reaction at the *para*-position, in comparison to  $\pi$ -complex with higher energy for the *ortho*-intermediate. Therefore, the complexes of 2,3,5-trimethylphenol derivatives with valerolactam and caprolactam are also more stable when the substitution takes place at *para*-position. Valerolactam forms a  $\sigma$ -complex at *para*-position, which has only a 0.5 kcal/mol (2.1 kJ/mol) lower energy than the  $\pi$ -complex at *ortho*-position. In the case of caprolactam the energy difference is even greater, 13.2 kcal/mol (55.4 kJ/mol) (Table 1).

In order to prove our suggestion that solvation has no significant influence on the efficiency of the quantum-chemical calculations, we calculated  $\sigma$ -complex energies for compound 6 in two solvents: chloroform and acetic acid by using IEF-PCM model. In chloroform the  $\sigma$ -complex at *para*-position is more stable, with the energy 2.45 kcal/mol (10.3 kJ/mol) lower than that for the complex at *ortho*-position. Very similar values were obtained for the calculations in acetic acid.



**Fig. 6** Zero-point corrected energies (kcal/mol) of the stationary points on the PES (shown relative to the reactants) for the gas phase lactamomethylation of 2,5-dimethylphenol 1 by pyrrolidone derivative.



**Table 1** Intermediate energies ( $\sigma$ -complexes for *para*-substitution and  $\pi$ -complexes for *ortho*-substitution) for compounds 3–8.

Compound	Intermediate energy $E$ , a.u.		Energy difference $E_{para}-E_{ortho}$ , a.u. (kcal/mol)
	<i>ortho</i> -substitution	<i>para</i> -substitution	
3	–710.772181	–710.775737	–0.003556 (–2.2)
4	–750.050906	–750.053234	–0.002328 (–1.5)
5	–789.326086	–789.327433	–0.001347 (–0.8)
6	–750.058059	–750.060571	–0.002512 (–1.6)
7	–789.337842	–789.338643	–0.000801 (–0.5)
8	–828.586048	–828.607080	–0.021032 (–13.2)

Noteworthy, there is no observable correlation between the energy differences of intermediates and the structures of reactants.

**Table 2** Intermediate energies for compounds 6 in chloroform and acetic acid.

Solvent	Intermediate energy $E$ , a.u.		Energy difference $E_{para}-E_{ortho}$ , a.u. (kcal/mol)
	<i>ortho</i> -substitution	<i>para</i> -substitution	
Chloroform	–750.112508	–750.116410	–0.004202 (–2.45)
Acetic acid	–750.116677	–750.120235	–0.003558 (–2.2)

Hence, gas-phase calculations give accurate results and may be used for the study of the reaction pathway.

Intermediate  $\sigma$ -complex at *para*-position has the energy 2.2 kcal/mol (9.4 kJ/mol) lower compared to *ortho*-isomer (Table 2).

#### 4. Conclusion

Six novel lactamomethyl derivatives of 2,5-dimethyl- and 2,3,5-trimethylphenols were synthesized with moderate yields of 51–68%. All products were characterized by FT-IR, NMR ( $^1\text{H}$ ,  $^{13}\text{C}$  and 2D: COSY, HSQC and HMBC) and elemental analysis. Calculated and experimental IR and NMR data showed good agreement. The reaction selectivity and yields were not affected by the solvent, as similar results were obtained in chloroform and acetic acid.

M06-2X method was used for quantum-chemical study of the lactamomethylation pathway. The substitution at *para*-position to the hydroxyl group produces the most stable  $\sigma$ -complexes and thus is preferable to *ortho*-substitution, which cannot proceed beyond  $\pi$ -complexes without input of energy.

#### 5. Authors contribution

SV: concept, synthesis and purification, structure elucidation (NMR), quantum-chemical calculations, manuscript preparation. OP: FT-IR experiments, data analysis, manuscript preparation. SB: data analysis, supervision, manuscript preparation. VK: concept, supervision, manuscript preparation. All authors have read and agreed to the final version of the manuscript.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.arabjc.2021.103424>.

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